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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/528,978	03/21/2000	R. Scott Obach	PC10244A	7527

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EXAMINER	
JIANG, SHAOJIA A	

ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 06/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/528,978	OBACH, R. SCOTT	
	Examiner	Art Unit	
	Shaojia A Jiang	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12/24/2003, 4/8/2004, 4/21/2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/24/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on December 24, 2003 has been entered.

This Office Action is a response to Applicant's request for continued examination (RCE) filed December 24, 2003, and amendment and response to the Final Office Action (mailed October 21, 2003), filed December 24, 2003, January 26, 2004, April 8, 2004, wherein claims 2-23 are cancelled, and claim 1 has been amended.

Currently, claim 1 is pending in this application.

Claim 1 is examined on the merits herein.

Applicant's amendment and remarks filed December 24, 2003 with respect to no new matter in the amended claim 1 has been fully considered and found persuasive since the specification as originally filed is seen to provide support for "a method of improving the pharmacokinetic profile.."(see page 1 line 4, and page 5 lines 20-23 of the specification).

Applicant's declarations of Ronald Scott Obach, Ph.D. (inventor), submitted December 24, 2003 and April 21, 2004 under 37 CFR 1.132, are acknowledged and will be further discussed below.

Applicant's amendment amending claim 1 and canceling claim 23, filed December 24, 2003 with respect to the rejection made under 35 U.S.C. 112 first paragraph for lack of scope of enablement of record stated in the Office Action dated October 21, 2003 has been fully considered and is found persuasive to remove this rejection since claim 1 has been limited to the particular drug and the particular CYP2D6 inhibitior. Therefore, the said rejection is withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 1 is rejected under 35 U.S.C. 112, first paragraph, for scope of enablement because the specification and evidence provided by Applicant's declarations of Ronald Scott Obach, Ph.D., submitted December 24, 2003 and April 21, 2004 under 37 CFR 1.132, while being enabling for the particular and specific compound (2S,3S)-2 phenyl-3-(2-methoxy-5-trifluoromethoxyphenyl)methylamino-piperidine, in combination

with quinidine employed in claimed method herein, does not reasonably provide enablement for (2S,3S)-2-phenyl-3-(2-methoxy-5-trifluoromethoxyphenyl)methylamino-piperidine, in combination with ajmalacine employed in claimed method herein.

The specification and evidence provided by Obach 's declarations, while being enabling for the employment for decreasing the elimination rate and lengthening half-life of (2S,3S)-2-phenyl-3-(2-methoxy-5-trifluoromethoxyphenyl)methylamino-piperidine by quinidine or ketoconazole (which is not the instantly claimed), does not reasonably provide enablement for improving the pharmacokinetic profile broadly of the particular combination herein. Note that pharmacokinetic profile is known to encompass various pharmacokinetic factors or parameters, as Applicant admits in the "Background" of the specification herein.

The instant specification and evidence provided by Obach 's declarations fail to provide sufficient information that would allow the skilled artisan to fully practice the instant invention without ***undue experimentation***. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

The nature of the invention: The instant invention pertains to a method of improving the pharmaceutical profile broadly of the particular combination herein.

The relative skill of those in the art: The relative skill of those in the art is high.

The predictability or unpredictability and the presence or absence of working examples and the quantity of experimentation necessary as discussed below:

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the evidence provided by Obach 's declarations shows that quinidine is capable of enhancing the pharmacological effect of (2S,3S)-2 phenyl-3-(2-methoxy-5-trifluoromethoxyphenyl)methylamino-piperidine, by inhibiting CYP2D6. However, the record such as the specification and declarations contain **no** clear and convincing evidence supporting the enablement for the claimed method employing (2S,3S)-2-phenyl-3-(2-methoxy-5-trifluoromethoxyphenyl)methylamino-piperidine, in combination with ajmalacine.

One of skill in the art would clearly recognize that quinidine and ajmalacine are separate and patentably distinct compounds since they do not share any common core structures (see their structures taught at page 4 of the instant specification); quinidine and ajmalacine are classified in different subclasses of class 514, for example, quinidine classified in 514/299, 311, whereas ajmalacine classified in 514/410, 413, 415. Thus, ajmalacine is not deemed to have same or substantial similar physiological activities

and properties as quinidine does. Therefore the enabling evidence for quinidine enhancing the pharmacological effect of (2S,3S)-2 phenyl-3-(2-methoxy-5-trifluoromethoxyphenyl)methylamino-piperidine in the declarations is not considered to represent ajmalacine having the same or substantially similar effects.

Moreover, as pointed out in the text book "Goodman & Gilman's The Pharmacological Basis of Therapeutics" regarding possible drug-drug interactions (9th ed, 1996) page 51 in particular. This book teaches that "The frequency of significant beneficial or adverse drug interactions is unknown" (see the bottom of the left column of page 51) and that "Recognition of beneficial effects and recognition of and prevention of adverse drug interactions require a thorough knowledge of the intended and possible effects of drugs that are prescribed" and that "The most important adverse drug-drug interactions occur with drugs that have serious toxicity and a low therapeutic index, such that relatively small changes in drug level can have significant adverse consequences" (see the right column of page 51) (emphases added).

In the instant case, in the absence of factual evidence for ajmalacine, one of skill in the art would not be able to fully predict possible beneficial or adverse drug-drug interactions occurring with the combination of ajmalacine and (2S,3S)-2 phenyl-3-(2-methoxy-5-trifluoromethoxyphenyl)methylamino-piperidine to be administered to a human. Thus, the teachings of the book clearly support that the instant claimed invention is highly unpredictable.

Thus, the specification fails to provide sufficient support of the use of ajmalacine in the instantly claimed method.

Genentech, 108 F.3d at 1366, states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the *Wands* factors, the case *University of California v. Eli Lilly and Co.* (CAFC, 1997) and *In re Fisher* (CCPA 1970) discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in *undue experimentation*, with no assurance of success.

Applicant's amendment amending claim 1 and canceling claims 11 and 23, the declarations under 37 CFR 1.132 and remarks submitted December 24, 2003, January 26, 2004 and April 21, 2004, have been considered and are sufficient to overcome the prior art rejection made under 35 U.S.C. 103(a) as being unpatentable over Benet et al. (5,567,592) and Hess (WO 96/14845) of record stated in the previous Office Actions dated October 21, 2003, for the following reasons. First, as Applicant asserts that in the claims, the purpose of quinidine and ajmalacine is to inhibit CYP2D6, and not for "mediating oxidative biotransformation for the major clearance mechanism in humans"; (2S,3S)-2 phenyl-3-(2-methoxy-5-trifluoromethoxyphenyl)methylamino-piperidine is drug for which the major clearance mechanism in humans is CYP2D6 mediated oxidative biotransformation, and therefore has a different purpose and function from quinidine and ajmalacine in the claimed method, i.e., enhancing the pharmacological effect of (2S,3S)-2 phenyl-3-(2-methoxy-5-trifluoromethoxyphenyl)methylamino-piperidine. Thus, the

instant case is distinguishable from *In re Kerkhoeven*, and therefore *In re Kerkhoeven* is not applicable to this case.

Second, Applicant's declarations under 37 CFR 1.132 with testing data and figures, in particular Figures 10, show a correlation between metabolism and inhibition of the same compound using the particular CYP2D6 inhibitor quinidine (Figure 10). Hence, the foregoing data further support that the (2S,3S)-2 phenyl-3-(2-methoxy-5-trifluoromethoxyphenyl)methylamino-piperidine has a different purpose from quinidine, and a surprising effectiveness of (2S,3S)-2 phenyl-3-(2-methoxy-5-trifluoromethoxyphenyl)methylamino-piperidine in combination with the CYP2D6 inhibitor, quinidine (see Figure 10 of the declaration submitted December 24, 2003 and the explanation at page 2 of the declaration submitted April 21, 2004).

Thus, the claimed method is not seen to be obvious over the cited prior art.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim 1 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 4 of copending Application No. 10/622,301.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application is drawn to the same or substantial similar method for improving some particular pharmacokinetic profile of the particular drug (1S, 2S)-1-(4-hydoxyphenyl)2(4-hydroxy-4-phenylpiperidin-1-yl)-1-propanol which is a CYP2D6 substrate by administering a CYP2D6 inhibitor, quinidine.

Thus, the instant claim 1 is seen to be obvious over the claims 1 and 4 of the copending Application No. 10/622,301.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner S. A. Jiang whose telephone number is 571.272.0627. The examiner can normally be reached on 9 am -5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571.272.0629. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

S. Anna Jiang, Ph.D.
Patent Examiner, AU 1617
June 2, 2004